Remarks

Claims 1-2 and 5-7 are pending.

35 U.S.C. § 112

The Office action rejected claims 1-2 and 5-7 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement.

Applicants request reconsideration and withdrawal of the rejection.

Claims 1-2 and 5-6

Claims 1-2 and 5-6 are drawn to a method of diagnosing or monitoring colon cancer in a subject, comprising the steps of detecting a level of a GPR49 polypeptide in a biological sample of a subject and comparing said level to a control level of said GPR49 polypeptide, wherein the GPR49 polypeptide is over-expressed in colon cancer tissues as compared to disease-free colon tissues.

The application teaches 63 genes "identified as uniquely overexpressed in colon cancer tissue relative to [a] panel of normal tissues" (paragraph [0433]). These genes have at least "a two-fold differential expression between normal and cancer tissue" (paragraph [0433]). One of these genes is GPR49 (paragraphs [0094], [0117] and [0118]). Applicants elected GPR49 in response to the restriction requirement of May 23, 2005.

Thus, the application demonstrates that GPR49 gene expression levels are indicative of the presence or absence of colon cancer and provides an actual example of the comparison of GPR49 gene expression levels in colon cancer subjects to control, healthy subjects. The application also teaches the production of antibodies to the polypeptides of the invention and the use of the antibodies in various *in vitro* and *in vivo* assays for the polypeptides.

The Office action nevertheless argues that the specification does not teach any working example that specifically detects GPR49 protein (Office action, page 4); that the application provides no objective evidence demonstrating overexpression of GPR49 protein in colon cancer (Office action, page 5), and that the expression of GPR49 protein has not been associated with colon cancer (Office action, page 5). The Office action concludes that one of skill in the art is

not enabled to use the claimed method for diagnosing or monitoring colon cancer by determining GPR49 protein (Office action, page 5).

According to M.P.E.P. § 2164.04, the USPTO has the initial burden to establish a basis for questioning that the specification enables the practice of the claimed invention:

> In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. . . . As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." . . .
>
> [T]he minimal requirement is for the examiner to give reasons for the uncertainty of the enablement. This standard is applicable even when there is no evidence in the record of operability without undue experimentation beyond the disclosed embodiments.

In the Office action, the enablement rejection appears to rely on the failure of the application to "demonstrat[e] over-expression of GPR49 protein in colon cancer." It is well established, however, that the absence of a working example is not a sufficient basis for rejecting a claim under the enablement requirement. M.P.E.P. § 2164.02 provides, for example, that "lack of working examples or lack of evidence that the claimed invention works as described should never be the sole reason for rejecting the claimed invention on the grounds of lack of enablement." An argument that the application does not demonstrate over-expression of GPR49 protein in colon cancer merely alleges a "lack of evidence that the claimed invention works as described" and is not a sufficient basis for an enablement rejection. Even a *prima facie* rejection requires objective evidence that one of skill in the art would require undue experimentation to practice the invention. As no such objective evidence has been provided in the Office action, Applicants request reconsideration and withdrawal of the rejection of claims 1-2 and 5-6.

Furthermore, Applicants submit that the application does indeed provide evidence that the claimed invention works as described. The application reports that the GPR49 gene demonstrates at least two-fold differential expression between normal and cancer tissue. While the application does not specifically report differences in levels of GPR49 *polypeptide* between normal and cancer tissue, the teachings in the application regarding the over-expression of the *gene* provide at least a reasonable basis for concluding that differences in levels of GPR49 polypeptide would exist and be useful in a method for diagnosing or monitoring colon cancer. It

is well known that a gene encodes a polypeptide and that increased expression of a gene can lead to increased levels of the encoded polypeptide. The Office action has neither challenged the teachings in the specification regarding the increased expression of the GPR49 gene nor provided a basis to conclude that the levels of GPR49 polypeptide remain unchanged. Applicants therefore respectfully request reconsideration and withdrawal of the rejection of claims 1-2 and 5-6.

As further supplemental evidence in support of the enablement of the claimed invention, Applicants enclose a declaration (the "Martinez Declaration") from Robert Vincent Martinez, Ph.D., one of the co-inventors of the claimed invention. In his declaration, Dr. Martinez testifies that "within a given tissue or cell under two different conditions, one of which is associated with transcriptional upregulation of a gene, I would expect a greater amount of encoded protein to result from a greater amount of mRNA" (Martinez Declaration, paragraph 4). In his declaration, Dr. Martinez the use of inducible promoters prior to January 2004 "to drive higher polypeptide expression in the cells and tissues into which they were introduced" (Martinez Declaration, paragraph 5), explaining that "the expectation, when using an inducible promoter, was the use of such a promoter would result not only in an increase in mRNA transcription from the gene to which the promoter was linked but also in a corresponding increase in the level of the polypeptide encoded by that mRNA" (Martinez Declaration, paragraph 5). Dr. Martinez goes on to testify that "[a]nalogously, a scientist in 2004 would have expected that upregulation of mRNA transcription from a specific gene in colon tissue (e.g. in colon cancer) would result in a greater amount of the polypeptide encoded by that mRNA in the colon tissue" (Martinez Declaration, paragraph 5).

In view of the Martinez Declaration, Applicants submit that based on the teachings in the specification, a scientist in 2004 would have expected the level of GPR49 polypeptide in colon cancer to be greater than the level of GPR49 polypeptide in disease-free colon tissue.

Applicants therefore respectfully request reconsideration and withdrawal of the rejection of claims 1-2 and 5-6.

Claim 7

Applicants request reconsideration and withdrawal of the rejection of claim 7 for all of the reasons applicable to claims 1-2 and 5-6.

Applicants further note that claim 7 is not limited to the use of GPR49 *polypeptides*; rather, the method of claim 7 uses the detection of an expression profile of one or more colon cancer *genes*, wherein one of said one or more colon cancer genes is GPR49. Although one could detect a GPR49 polypeptide when detecting an expression profile of a GPR49 gene, one could also detect a GPR49 nucleic acid. Applicants submit that the application provides direct evidence that the invention of claim 7 works as described. For that reason, in addition to all of the reasons applicable to claims 1-2 and 5-6, Applicants request reconsideration and withdrawal of the rejection of claim 7.

CONCLUSION

Claims 1-2 and 5-7 are pending. Applicants respectfully request withdrawal of the outstanding rejection and allowance of the claims. Applicants invite the Examiner to call the undersigned attorney to address any remaining issues.

Respectfully submitted,

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